DOCKET NO.: ISIS-5207 **PATENT**

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

In re Application of: **Baker, B.F. et al.** Confirmation No.: **5280**

Serial No.: **10/701,236** Group Art Unit: **1635**

Filing Date: **November 4, 2003** Examiner: **Chong, Kimberly**

For: **SUGAR SURROGATE-CONTAINING OLIGOMERIC COMPOUNDS AND COMPOSITIONS FOR USE IN GENE MODULATION**

APPELLANTS' APPEAL BRIEF PURSUANT TO 37 C.F.R. § 41.37

This Appeal Brief is in response to the final office action of March 16, 2011. The Notice of Appeal was filed September 14, 2011. Since this Appeal Brief is being filed on or before April 16, 2012 (April 14, 2012 being a Saturday) with a five month extension of time it is timely.

1. REAL PARTY IN INTEREST

The real party in interest is the assignee of record for this application, Isis Pharmaceuticals, Inc., 2855 Gazelle Ct.,, Carlsbad, CA 92010.

2. RELATED APPEALS AND INTERFERENCES

Application No. 10/701,264--appeal brief filed March 22, 2012.

Application No. 10/701,265--Notice of Appeal filed September 30, 2012.

Application No. 11/054,848—appeal brief filed April 30, 2010

Application No. 10/701,007—appeal brief filed April 28, 2010

Application No. 10/860,265—appeal brief filed April 30, 2010

3. STATUS OF CLAIMS

Rejected: claims 1, 71-73 and 76-79

Allowed: none

Withdrawn: none

Objected to: none

Canceled: claims 2-70, 75 and 75

Appealed: claims 1, 71-73 and 76-79

4. STATUS OF AMENDMENTS

No amendment was filed after the final office action of March 16, 2011.

5. SUMMARY OF CLAIMED SUBJECT MATTER

The following summary is for the purpose of complying with the provisions of 37 C.F.R. § 41.37(c)(1)(v). The entire disclosure should be reviewed to obtain a complete understanding of the claimed subject matter.

Claim 1

Claim features	Exemplary description in the specification
A composition comprising a duplex consisting of a first and a second chemically synthesized oligonucleotide, wherein:	**[0023]; [0132]-[0136]**
each of the first and the second chemically synthesized oligonucleotides is from 17 to 25 linked nucleosides in length;	**[0026]; [0128]-[0131]; [0264]-[265]**
the first chemically synthesized oligonucleotide is 100% complementary to the second chemically synthesized oligonucleotide and to a selected target mRNA;	**[0039]; [0048]-[0050]; [0096]**
the first chemically synthesized oligonucleotide and the second chemically synthesized oligonucleotide are not covalently linked to each other;	**[0264]-[265]**
at least one of the first and second chemically synthesized oligonucleotides comprises a plurality of 2'-hydroxy-pentofuranosyl sugar moieties; and	**[0137]**
each of the first and the second chemically synthesized oligonucleotides comprises at least one modified nucleoside comprising a sugar surrogate.	**[0023]; [0028]-[0038]**

6. GROUNDS OF REJECTION TO BE REVIEWED ON APPEAL

Claims 1, 71 to 73, and 76 to 79 have been rejected under 35 U.S.C. § 103(a) as allegedly rendered obvious by Wyatt, *et al.*, *Nucleic Acids Res.*, 1989, 17, 7833-7842 (Wyatt article), Monia, *et al.*, *J. Biol. Chem.*, 1993, 268, 14514-14522 (Monia article), Manche, et al., *Mol. Cell Biol.*, 1992, 12, 5238-5248 (Manche), and U.S. Patent Number 5,801,154 (Baracchini).

7. ARGUMENT

1. Legal principles

As set forth in *KSR Int'l Co. v. Teleflex Inc.*, 127 S.Ct. 1727, 1741 (2007).

> [A] patent composed of several elements is not proved obvious merely by demonstrating that each of its elements was, independently, known in the prior art. Although common sense directs one to look with care at a patent application that claims as innovation the combination of two known devices according to their established functions, it can be important to identify a reason that would have prompted a person of ordinary skill in the relevant field to combine the elements in the way the claimed new invention does.

Thus, it is impermissible to use the claimed invention as an instruction manual or "template" to piece together the teachings of the prior art so that the claimed invention is rendered obvious. *See In re Fritch*, 972 F.2d 1260, 1266 (Fed. Cir.1992).

2. Analysis

Before reviewing the pending obviousness rejection, the Board should appreciate that this application has been pending since November, 2003. In the ensuing eight years, claims in this and related applications have been serially rejected under 35 U.S.C. §§ 112, 101, 102, and most recently, Section 103. Appellants have repeatedly replied at great expense to office action after office action, overcoming one set of rejections, only to be confronted with a new set. In response to the previous rejections under 35 U.S.C. § 103, applicants provided a Declaration from Dr. David Corey, a noted scientist who has been active in the field since the time of the original filing. That declaration sets forth in detail the factual basis for why one of skill in the art would not have found the claimed oligomeric compounds obvious. The examiner dismissed this declaration, however, simply labeling it non-persuasive. Hoping at long last to resolve this application, applicants then appealed to the Board of Patent Appeals and Interferences and

submitted a request for a pre-appeal brief conference that also sets forth in detail why the claimed oligomeric compounds would not have been obvious at the time of the invention. After the notice of appeal and request for a pre-appeal brief conference were filed, rather than allowing the claims, or even allowing the application to proceed to appeal to finally resolve the outstanding issues, the examiner instead re-opened prosecution, with allegedly "new" grounds for once again rejecting the claims as obvious. The present rejections rely on several references already addressed by appellants and discussed by Dr. Corey. Those previously discussed references are now combined with new, largely duplicative references, not previously cited throughout the long prosecution history of this application. As explained below, these "new" rejections fail for the same fundamental reason as the previous obviousness rejections: the examiner has still not provided a reason why one of skill in the art would have made the claimed compounds prior to invention by the applicants.

a. The obviousness rejection is based upon concepts nowhere found in the applied references

The pending obviousness rejection can be aptly characterized as a "concept" rejection. This is seen in that the examiner does not start with a prior art composition that comprises a duplex consisting of a first and a second chemically synthesized oligonucleotide and propose changes to that core structure based upon teachings from the prior art. Rather, the examiner first constructs a ***hypothetical*** duplex from assorted teachings of Wyatt, Monia and Manche. Office action of June 22, 2010 at 5-6. Then the examiner proposes to modify this ***hypothetical*** duplex based upon additional teachings of Monia and additional teachings of Baracchini. The error in the examiner's construction of this rejection is believed to be clear.

The only glue that holds this rejection together is the present disclosure of the invention. If one views the examiner's proposed combination of references apart from the present disclosure and claims, it is seen that there is no reason except for impermissible hindsight to construct the examiner's hypothetical duplex. Neither Wyatt, Monia nor Manche suggest the formation of the examiner's hypothetical duplex because each of those references, as discussed below, describes basic research into a particular aspect of cellular biology or oligonucleotide activity. None of these references suggest that its specific disclosure be modified in the way the

examiner now proposes. This is strong evidence of the hindsight nature of the present obviousness rejection.

b. The examiner errs by ignoring record evidence of non-obviousness

While it is believed that the applied references do not establish a *prima facie* case of obviousness, in the event in may be considered that they do so, the examiner has ignored record evidence relevant to the present obviousness determination, i.e., the Declaration of David Corey executed August 5, 2009. As mentioned, Dr. Corey's declaration was first presented in response to a previous obviousness rejection that was withdrawn in lieu of the present obviousness rejection. However, to the extent Dr. Corey discusses Manche and Baracchini; the declaration must be considered by the examiner. As stated in *In re Hedges*, 783 F.2d 1038, 1039 (Fed. Cir. 1986):

> If a *prima facie* case is made in the first instance, and if the applicant comes forward with reasonable rebuttal, whether buttressed by experiment, prior art references, or argument, the entire merits of the matter are to be reweighed. *In re Piasecki*, 745 F.2d 1468, 1472 (Fed. Cir. 1984).

Dr. Corey explains that Manche teaches away from the present composition as it provides no reason (1) to use a duplex having less than 33 base pairs (Corey Decl. at ¶ 16), (2) no reason to provide 100% complementarity (Corey Decl. at ¶ 17) and (3) no reason to make chemically modified oligonucleotides as the duplexes of the reference were "synthesized enzymatically, not through chemical synthesis and do not contain any chemical modification" (Corey Decl. at ¶ 18). Dr. Corey concluded that Manche "would not have prompted on to make the claimed compounds and that the claimed compounds would have been unsuitable for use in the research described in Manche. Corey Decl. at ¶ 19. Dr. Corey also provides a detailed analysis of Baracchini and explains why that reference does not teach or suggest the claimed compounds. Corey Decl. at ¶¶ 20-24.

c. The applied reference teach away from their combination as proposed by the examiner

It is axiomatic that a "prior [art reference] must be considered in its entirety, i.e., as a whole, including portions that would lead away from the invention in suit." *Panduit Corp. v. Dennison Mfg. Co.*, 810 F.2d 1561, 1568 (Fed.Cir.1987). Here the examiner has failed to consider those portions of the applied references that lead away from the claimed compositions.

Dr. Corey explains in his declaration how Manche and Baracchini teach away from combining their teachings in the manner proposed by the examiner. Therefore, Dr. Corey's declaration provides strong evidence that the pending obviousness rejection is based upon impermissible hindsight instead of the teachings of the references themselves.

d. The applied references considered individually or together do not suggest the claimed subject matter as a whole.

Specifically, those of ordinary skill in the art would not have had a reason at the time of the invention to produce duplexes of fully complementary oligomeric compounds consisting of 17 to 25 linked nucleosides in which each strand of the duplexes comprises at least one modified nucleoside comprising a sugar surrogate, in view of the description provided in the cited references.

In this regard, Wyatt does not describe or suggest fully complementary oligomeric compounds consisting of 17 to 25 linked nucleosides in which each strand of the duplex comprises at least one modified nucleoside comprising a sugar surrogate, and nothing in Wyatt would have prompted those of ordinary skill in the art to produce such duplexes. Rather, Wyatt describes duplexes of complementary 14-mer oligoribonucleotides, and also describes 14-mer oligoribonucleotide duplexes in which one or two 2'-deoxyribonucleotides were substituted for the ribonucleotides in one or both of the strands. The duplexes were used in *in vitro* experiments aimed towards determining the structural requirements of RNase V_1. In these experiments, the oligoribonucleotide duplexes and deoxy-substituted duplexes were incubated *in vitro* with the RNase V_1 and buffer, and the article reports that the deoxy substitutions reduced cleavage by RNase V_1. Significantly, no other nucleases were present during the RNase V_1 reactions.

Wyatt also describes experiments designed to determine the structural requirements for *E. coli* RNase H. Those experiments utilized 14-mer oligoribonucleotides with or without one or two 2'-deoxyribonucleotide substitutions hybridized to complementary 17-mer deoxyoligoribonucleotides or hybridized to complementary 17-mer oligoribonucleotides having one or two 2'-deoxyribonucleotide substitutions. In the RNase H reactions, the substrates were incubated *in vitro* with RNase H and buffer, and the reactions did not contain any other nucleases. Wyatt indicates that deoxy substitutions in the RNA strand of the RNA:DNA hybrids inhibited

cleavage by RNase H. Significantly, Wyatt provides no teaching or suggestion that would have prompted those skilled in the art to incorporate at least one modified nucleoside comprising a sugar surrogate into both strands of a duplex of oligomeric compounds. Nothing about the design or nature of the experiments described in Wyatt would have provided a reason to introduce modified nucleosides comprising sugar surrogates into *both* strands of an oligomeric compound duplex.

The remaining references fail to supply this missing teaching or suggestion, and thus fail to compensate for the deficiencies of Wyatt. Monia fails to provide any description that would have prompted those of ordinary skill in the art to incorporate at least one modified nucleoside comprising a sugar surrogate into both strands of an oligomeric compound duplex. Instead, Monia describes 17-mer oligonucleotides having a central gap region of 2'-deoxynucleotides and having 5' and 3' wing regions of 2'-OMe substituted nucleotides. *Id.,* Fig. 1. These gapmers were hybridized to the following complementary RNAs:

1. A synthetic, end-labeled 25-mer RNA corresponding to Ha-*ras* RNA. The resulting duplex was used in *in vitro* melting experiments;

2. A 47-mer Ha-*ras* RNA hairpin. The resulting duplex was used in *in vitro* RNase activation experiments; and

3. Full-length Ha-*ras* mRNA, after introduction of the gapmer into HeLa cells that had been transfected with an Ha-*ras* expression plasmid, to determine the antisense activity of the gapmer.

Monia also describes hybridization of 11-mer, 13-mer, or 15-mer 2'-OMe gapmers to end-labeled 25-mer RNAs corresponding to Ha-*ras* RNA. The resulting duplexes was used in *in vitro* melting experiments. *Id.*, Fig. 8A.

Finally, Monia describes melting experiments that utilized 17-mer gapmers having a central, 2'-deoxy region and 5' and 3' wing regions of either 2'-deoxy, 2'-O-pentyl, 2'-O-propyl, 2'-O-methyl, or 2'-fluoro groups hybridized to 25-mer RNAs corresponding to Ha-*ras* RNA. *Id.*, Table II. These gapmers were also introduced into HeLa cells that had been transfected with a Ha-*ras* expression plasmid to determine their antisense activity against full-length Ha-*ras* mRNA.

Significantly, Monia contains no teaching or description that would have prompted those of ordinary skill in the art to incorporate at least one modified nucleoside comprising a sugar surrogate into *both* strands of an oligomeric compound duplex. The *in vitro* melting and RNase activation experiments described in the Monia article utilized duplexes in which only one strand contained chemical modifications, and there would have been no reason to utilize substrates having chemical modifications in both strands in such experiments. Furthermore, in the experiments in which the antisense activity of the single-stranded gapmers was analyzed, *duplexes* were not introduced into HeLa cells, but, rather, single-stranded gapmers were introduced, and their activity against unmodified, full-length mRNA target was determined. *See, e.g.,* Fig. 6.[1] Accordingly, nothing about the design or objective of the experiments described in Monia would have prompted those of ordinary skill in the art to incorporate chemical modifications into both strands of a duplex of oligomeric compounds, much less incorporate at least one modified nucleoside comprising a sugar surrogate into both strands of a duplex, as claimed.

Similarly, as discussed at length previously during prosecution of this application and as explained by Dr. Corey in his declaration, Corey Decl. at ¶ 16-19, Manche also fails to provide such a teaching or suggestion. Instead, Manche describes short RNA duplexes that were used as substrates in experiments designed to elucidate the mechanism of activation of interferon-induced protein kinase DAI. Specifically, the experiments involved binding DAI to RNA duplexes of 15, 23, 34, 40, 55, 67, 85, or 104 nucleotides *in vitro*. *Id.*, Fig. 1A The RNA duplexes were not chemically modified, and as pointed out by Dr. Corey in his declaration, *id.,* nothing about the nature or aim of the experiments described in Manche provides any reason that would have prompted those of ordinary skill in the art to produce chemically modified RNA duplexes, much less duplexes having at least one modified nucleoside comprising a sugar surrogate in both strands, as claimed.

Finally, as discussed by Dr. Corey in his declaration, Corey Decl. at ¶¶ 20-24, Baracchini also fails to provide such a reason. Instead, Baracchini describes single-

[1] The examiner's observation that Monia used duplexes in cell extract experiments, Office action of March 16, 2011 at 4, is not relevant as the fact remains that the Monia experimental work involving antisense activity was conducted with single-stranded gapmers.

stranded antisense deoxynucleotides targeted against mRNA encoding multidrug resistance associate protein (MRP). Although Baracchini describes chemical modification of antisense deoxynucleotides, as explained by Dr. Corey, *id.*, Baracchini does not describe or suggest any reason to introduce chemical modifications into *duplexes* of oligomeric compounds consisting of 17 to 25 linked nucleosides.

Those of ordinary skill in the art therefore would have had no reason to produce duplexes of fully complementary oligomeric compounds consisting of 17 to 25 linked nucleosides in which each strand of the duplexes comprises at least one modified nucleoside comprising a sugar surrogate before applicants' invention in view of the description provided in the cited references, when considered in combination in view of the state of the art at that time. The claimed oligomeric compounds therefore would not have been obvious before appellants' invention.

The examiner asserts, however, that "the person of ordinary skill in the art would have reason to incorporate 2'-sugar groups into the duplex because these references teach that nucleolytic degradation is a problem for nucleic acids and that stabilization of a duplex with modified nucleotides provide resistance to nucleases." Office action dated June 22, 2010 at 6. Contrary to the examiner's assertion, those of ordinary skill would *not* have had a reason to incorporate chemical modifications, such as sugar surrogates, into *both* strands of an oligomeric compound duplex at the time of the invention because the experiments described in the cited references do not involve conditions in which undesired nucleolytic degradation of such duplexes could have occurred. In the *in vitro* experiments described in the references, such as the RNase H and RNase V_1 digestion experiments, in accordance with the experimental designs used, undesired nucleases were not present during the reactions that could have potentially degraded the substrates. As discussed above, only the RNase H and RNase V_1 endonucleases were present in the reaction mixtures, and no other enzymes were present. Furthermore, in the experiments in which nucleic acids were introduced into cells or were treated with cellular extracts, *single-stranded* oligonucleotides targeted against full-length mRNAs were used in such experiments, and double-stranded duplexes were not utilized. None of the references therefore describes experiments in which double-stranded nucleic acids were introduced into an environment in which undesired nucleolytic degradation of the duplexes could

have occurred. Moreover, the goal of the cited research was to determine the effect of modulation of certain parameters on the cleavage of natural unmodified RNA by the ribonucleases being investigated. Accordingly, one would not introduce modifications into that RNA. The Examiner offers no credible reason derived from the cited references for introducing modifications into the RNA strand of the hypothetical duplexes.

Contrary to the examiner's assertion, the applied references fail to provide any reason that would have prompted those of ordinary skill in the art to protect both strands of a duplex of oligomeric compounds of the length claimed against nucleolytic degradation by introducing chemical modifications into both strands of such duplexes. Dr. Corey explained that such compounds would not have been particularly suitable for the research described in the previously cited references, including Manche and Baracchini. Likewise, there would have been no reason why one skilled in the art would have used such compounds for the research described in the additional, newly-cited references. Because none of the applied reference, nor all of them combined, describe research for which one skilled in the art would have had a reason to make the claimed oligomeric compounds, such compounds would not have been obvious at the time of the invention.

Conclusion

Appellants believe that the pending claims are directed to non-obvious subject matter and for the reasons set forth above respectfully request that the examiner's conclusion to the contrary be determined to be in error and that the pending obviousness rejection be reversed.

Date: April 5, 2012

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CLAIMS APPENDIX

1. (previously presented) A composition comprising a duplex consisting of a first and a second chemically synthesized oligonucleotide, wherein:

each of the first and the second chemically synthesized oligonucleotides is from 17 to 25 linked nucleosides in length;

the first chemically synthesized oligonucleotide is 100% complementary to the second chemically synthesized oligonucleotide and to a selected target mRNA;

the first chemically synthesized oligonucleotide and the second chemically synthesized oligonucleotide are not covalently linked to each other;

at least one of the first and second chemically synthesized oligonucleotides comprises a plurality of 2'-hydroxy-pentofuranosyl sugar moieties; and

each of the first and the second chemically synthesized oligonucleotides comprises at least one modified nucleoside comprising a sugar surrogate.

2-70. (Canceled)

71. (previously presented) The composition of claim 1, wherein at least one of the first and the second chemically synthesized oligonucleotides comprises at least one phosphorothioate linkage.

72. (previously presented) The composition of claim 1, wherein each of the first and the second chemically synthesized oligonucleotides comprises at least one phosphorothioate linkage.

73. (previously presented) The composition of claim 1, wherein at least one sugar surrogate is selected from among a pyrrolidine nucleoside, a morpholino nucleoside, a cyclobutyl nucleoside, and a peptide nucleic acid nucleoside.

74-75. (Canceled)

76. (previously presented) The composition of claim 1, wherein each of the first and the second chemically synthesized oligonucleotides comprises a plurality of 2'-hydroxy-pentofuranosyl sugar moieties.

77. (previously presented) The composition of claim 1, wherein each of the first and the second chemically synthesized oligonucleotides comprises at least two modified nucleosides each independently comprising a sugar surrogate.

78. (previously presented) The composition of claim 1, wherein the mRNA is a mammalian mRNA.

79. (previously presented) The composition of claim 1, wherein the mRNA is a human mRNA.

EVIDENCE APPENDIX

A copy of the declaration filed under 37 CFR § 1.132 of Dr. David Corey is attached as Exhibit A.

RELATED PROCEEDINGS APPENDIX

None.